Remarks

Amendments to the Claims

Claims 1 and 10 have been amended to correct the grammar.

Rejections Under 35 U.S.C. § 103

Claims 1-4 and 6-10 were rejected under 35 U.S.C. § 103 as obvious over Skraly, Polyhydroxyalkanoates Produced by Recombinant E. coli, Poster Engineering Foundation Conference: Metabolic Engineering 1998 ("Skraly"), Madison, et al. Metabolic engineering of poly(3-hydroxyalkanoates): from DNA to plastic. Microbiol. Mol. Biol. Rev. 63(1):21-53 (1999) ("Madison") and BRENDA database ("Brenda database"). Applicants traverse this rejection.

Legal Standard

When applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

(a) determining the scope and contents of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating evidence of secondary consideration.

Graham v. John Deere, 383 US 1, 17-18, 148 USPQ 459,467 (1966). These four factors are traditionally referred to as the Graham factors. The Graham factors were recently affirmed bythe U.S. Supreme Court. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court did not totally reject the use of "teaching, suggestion, or motivation" as a factor in the obviousness analysis. Rather, the Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

In response to the KSR decision, the Deputy Commissioner for the USPTO issued a memorandum stating: "Therefore, in formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from Margaret A. Forcarino to Technology Center Directors (May 3, 2007).

Additionally, it is well known that references relied upon to support a rejection under 35 U.S.C. § 103 must provide an enabling disclosure, i.e., "they must place the claimed invention in the possession of the public." *Application of Payne*, 606 F.2d 303, 314, 203 U.S.P.Q. 245 (C.C.P.A. 1979); *see Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 13 U.S.P.Q.2d 1301 (Fed. Cir. 1989). A publication that is insufficient as a matter of law to constitute an enabling reference may still be relied upon, but only for what it discloses. *See Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-652, 223 U.S.P.Q. 1168 (Fed. Cir. 1984); *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991).

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *See In re Geiger* . 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

The Prior Art

Skraly

Skaly is a poster session reviewing methods for genetically engineering organisms to make a variety of different PHAs. Page 7 indications that 1,3-propanediol and 1,5 pentanediol can be used as feedstocks to make p(3HP) and P(3HP-co-5HV) (page 7). At page 9 there is a reference to using a 1,3-propanediol oxidoreductase to synthesize PHB-co-3HP from glycerol and PHB-co-3HV from 1,2-propanediol.

Madison

Madison is a review article discussing metabolic engineering of organisms to produce poly(3-hydroxyalkonates). The examiner acknowledges in the Office Action that Madison does not disclose the claimed elements. The Examiner states that Madison is cited to show the level of skill in the art in that recombinant organisms can be engineered to express the genes necessary. There is no teaching leading one to conclude that one should, or could make the

claimed organisms and produce polymers from the claimed monomers. Madison does teach one that PHAs made by bacteria can have a low, mid or high molecular weight. This is a far cry from a teaching that one should start with diols not described in any of the references, use enzymes not described in any of the references, and expect to make high molecular weight PHAs as claimed.

BRENDA database

The BRENDA database discloses several diol reductases and contains hyperlinks to the sequences for several or the enzymes. Notably, the database is not dated either on the document or on the PTO-892. The Examiner acknowledges that BRENDA does not disclose diol reductases that act on 1,5-pentanediol, 1,6-hexanediol, and 1,2-ethanediol.

Analysis

The examiner has done an excellent job of taking the claims in issue, then searching for prior art that discloses some of the claimed elements, then concluding that since they all generally relate to making polyhydroxyalkanoates, that it is obvious to combine. This is not an appropriate analysis under 35 U.S.C. § 103. The art must disclose each claimed element, there must be motivation to combine, if not in the art, then within the skill and knowledge of one in the art, with a reasonable expectation of success. One cannot use hindsight. A claimed method is not obvious when it achieves more than what is obtained with the separate elements, alone or in combination.

1. Claim 1 is Nonobvious in view of the Prior Art

Claim 1 recites:

A method for producing polyhydroxyalkanoates comprising

providing organisms selected from the group consisting of bacteria, plants, and yeast,

which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase,

wherein the organisms are genetically engineered to express enzymes which are active in bacteria or plants, selected from the group consisting of ***diol oxidoreductase and aldehyde dehydrogenase,***

wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of **4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate**, and

culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

Skraly does not disclose a method that can convert diols into hydroxyalkanoate monomers selected from the group consisting of **4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate.** The only monomers that Skraly describes using are PHB-co-3HP (from 3-hydroxybutyrate and 3-hydroxypropionate) and PHB-co-3HV (from 3-HB and 3-hydroxyvalerate). None of these are claimed.

One skilled in the art knows that one must provide both (1) an appropriate substrate and (2) appropriate enzymes which can utilize the provided substrate to produce (3) a desired product. It is not an inherent outcome that merely because an organism has been shown to produce the desired product, or has been provided with an appropriate substrate, or even that an

organism expresses one or more of the required enzymes, that one will produce the desired product.

The examiner has drawn conclusions that one could read into the disclosure that other diols could be utilized, but no evidence for such a conclusion is found in the reference, much less what enzymes would be required and whether they would have the appropriate specificity. There is no basis to conclude that one would make the substitutions in feedstock that applicants have done, to produce the claimed polymers, based on this disclosure. Indeed, it was two years later that applicants, who worked with Skraly, et al., filed this application, having isolated the necessary materials, engineered the cells and demonstrated that it was possible.

Madison does not make up for these deficiencies. No where is there any teaching that one could or should make **a high molecular weight PHA** from **diols** converted into **the claimed monomers**. The examiner has not even identified where such polymers are described. Even as to the molecular weight range, this is not for polymers of the claimed monomer composition, but conventional PHB polymers. As noted in the Office Action, Madison is cited to show the state of the art.

The Brenda database does not make up for this. The Brenda database shows several enzymes and their substrates. Applicants have told those skilled in the art how to practice their claimed method; the standard is not whether having the answer in hand one can support the conclusion. This is the examiner's approach, however.

One also cannot just "lump" the claims together, focusing solely on the elements in the independent claims, and completely fail to examine the elements of the dependent claims. This is as unacceptable as using hindsight. Applicants have disclosed in their application the specific enzymes, diols, and monomers to be used to produce specific polyhydroxyalkanoates. In *Loctite*

Corp. v. Ultraseal Ltd. (1985), the Federal Circuit stressed that "the need for express Graham findings takes on an especially significant role because of an occasional tendency of district courts to depart from the Graham test, and from the statutory standard of unobviousness that it helps determine, to the tempting but forbidden zone of hindsight."

It is impermissible to use the inventor's disclosure as a "road map" for selecting and combining prior art disclosures. In *Interconnect Planning Corp. v. Feil,* 774 F.2d 1132, 227 USPQ 543 (Fed. Cir. 1985) the Federal Circuit noted that "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." In *In re Fritch,* 972 F.2d 1260, 23 USPQ2d 1780 (Fed. Cir. 1992), it noted: "[I]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. ... This court has previously stated that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" Applicants respectfully submit that the rejection should be withdrawn.

2. Claim 2 is Nonobvious In View of the Prior Art

None of the specific diols and monomer compositions of claim 2 are at all described in the prior art cited by the examiner. 1,6-hexanediol and the hydroxyalkanoate monomer 6-hydroxyhexanoate recited in claim 2 are not disclosed or suggested in the prior art relied upon by the Examiner.

3. Claim 3 is Nonobvious In View of the Prior Art

None of the specific diols and monomer compositions of claim 3 are at all described in the prior art cited by the examiner. 1,5-pentanediol and the hydroxyalkanoate monomer 5-

hydroxyvalerate recited in claim 3 are not disclosed or suggested in the prior art relied upon by the Examiner.

4. Claim 4 is Nonobvious In View of the Prior Art

None of the specific diols and monomer compositions of claim 4 are at all described in the prior art cited by the examiner. 1,4-butanediol and the hydroxyalkanoate monomer 4-hydroxybutyrate recited in claim 4 are not disclosed or suggested in the prior art relied upon by the Examiner.

5. Claim 6 is Nonobvious In View of the Prior Art

None of the specific diols and monomer compositions of claim 6 are at all described in the prior art cited by the examiner. 1,2-ethanediol and the hydroxyalkanoate monomer 2-hydroxyethanoate recited in claim 6 are not disclosed or suggested in the prior art in the prior art relied upon by the Examiner.

6. Claim 7 is Nonobvious In View of the Prior Art

None of the specific diols and monomer compositions of claim 7 are at all described in the prior art cited by the examiner. 1,2-propanediol and the hydroxyalkanoate monomer 2-hydroxypropionate recited in claims 7 are not disclosed or suggested in the prior art relied upon by the Examiner. Moreover, the Examiner is impermissibly relying on hindsight analysis to pick and chose different pieces of art to cobble together and allege that the claimed subject matter is obvious.

7. Claim 8 is Nonobvious In View of the Prior Art

Claim 8 depends form claim 1 and further defines the method of claim 1 as having the organism express polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase. The cited references do not disclose or suggest a method for producing

polyhydroxyalkanoates using organisms that express polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase that can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, and wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

8. Claim 9 is Nonobvious In View of the Prior Art

Claim 9 depends from claim 8 and further defines the organism as selected from the group consisting of *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., and *Comamonas* spp. The cited references do not disclose or suggest a method for producing polyhydroxyalkanoates using *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., or *Comamonas* spp. that express polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase that can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, and wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

9. Claim 10 is Nonobvious In View of the Prior Art

Claim 10 defines a system for making polyhydroxyalkanoates using organisms selected from the group consisting of bacteria, plants, and yeast , which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-

CoA reductase, and PHA synthase, wherein the organism is genetically engineered to express polynucleotides that encode enzymes, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, wherein the monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

As discussed above, Skraly does not disclose a system that can convert diols into hydroxyalkanoate monomers selected from the group consisting of **4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate.** The only monomers that Skraly describes using are PHB-co-3HP (from 3-hydroxybutyrate and 3-hydroxypropionate) and PHB-co-3HV (from 3-HB and 3-hydroxyvalerate). None of these are claimed. The examiner has drawn conclusions that one could read into the disclosure that other diols could be utilized, but no evidence for such a conclusion is found in the reference, much less what enzymes would be required and whether they would have the appropriate specificity. There is no basis to conclude that one would make the substitutions in feedstock that applicants have done, to produce the claimed polymers, based on this disclosure.

Madison, as noted above, does not make up for these deficiencies. No where is there any teaching that one could or should make a high molecular weight PHA from diols converted into the claimed monomers. The examiner has not even identified where such polymers are

described. Even as to the molecular weight range, this is not for polymers of the claimed monomer composition, but conventional PHB polymers.

The Brenda database does not make up for this deficiency. Applicants have told those skilled in the art how to practice their claimed method; the standard is not whether having the answer in hand one can support the conclusion. This is the examiner's approach, however.

In summary, the prior art neither discloses the claimed elements nor the motivation to combine as applicants have done, much less with a reasonable expectation of success.

For the foregoing reasons, claims 1-4 and 6-10 are patentable.

Respectfully submitted,

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